Bevacizumab in the primary treatment of epithelial ovarian cancer – some comments on the latest results

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Abstract: Adding the angiogenesis inhibitor bevacizumab to initial standard chemotherapy followed by bevacizumab alone as maintenance therapy prolongs progression-free survival (PFS) time significantly but modestly in women with advanced epithelial ovarian cancer. This finding has been reported consistently by two phase III trials, GOG-218 and ICON 7. At present, overall survival (OS) data are immature. Therefore, no recommendation can be made yet how to best incorporate bevacizumab in the front-line treatment of advanced ovarian cancer. Members of the gynecological cancer working group of the Swiss Group for Clinical Cancer Research (SAKK) and other specialists have discussed the latest findings with bevacizumab in ovarian cancer and their consequences for clinical practice. Ovarian cancer is the seventh most frequent cancer in women worldwide (1). Its incidence rates are highest in the western world, where it is the leading cause of death from gynecological malignancies (2, 3). Patients with stage III and IV ovarian cancer require a combined approach of surgery and chemotherapy. Primary debulking surgery plays a key role and the final outcome is highly dependent on the results achieved with the initial surgery: a residual tumor of >1 cm was found to be associated with a median overall survival of 12–16 months, while a longer median overall survival has been reported in patients with no macroscopic residual disease (4). The ultimate goal of surgery is cytoreduction to microscopic disease, the term optimal cytoreduction being reserved for those cases with no macroscopic residual disease. The standard first-line chemotherapy for advanced ovarian cancer usually contains a taxane and a platinum agent for six cycles (5-8). The response rate for this treatment is approximately 75%. However, 65% of these patients will develop tumor progression in the first three years after diagnosis. Over the past ten years, the only improvement in overall survival has been reported with the introduction of a dose dense schedule of paclitaxel (9) or by the use of local ip treatment in selected patients (10); the addition of a third cytotoxic to standard chemotherapy has not showed any significant advantage over the established first-line chemotherapy (11, 12).

Bevacizumab in the primary treatment of epithelial ovarian cancer* – some comments on the latest results

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Identification of new targets

Better knowledge of the molecular biology has prompted new treatment approaches, such as inhibition of angiogenesis. In ovarian cancer, the vascular endothelial growth factor (VEGF) is overexpressed and is associated with ascites formation and malignant progression (13, 14). In preclinical studies with anti-VEGF therapy, delayed tumor progression, resolution of malignant effusions, and synergy with cytotoxic agents have been demonstrated (15).

Bevacizumab is a recombinant, humanized antibody to VEGF, which inhibits tumor angiogenesis and which has shown promising activity in recurrent ovarian cancer as a single agent and in combination with chemotherapy (15-17). Further angiogenesis inhibitors are investigated in clinical trials (phase I and II) in this disease e.g. cediranib, pazopanib and AMG 386.
To understand the role of bevacizumab in the initial treatment of advanced ovarian cancer, two groups of academic investigators, the Gynecologic Oncology Group (GOG) and the Gynecologic Cancer Intergroup (GCIG), conducted separate phase III trials with a total accrual of 3,401 patients. Both trials, GOG-218 and ICON 7, assessed the effect of the addition of bevacizumab to standard therapy and the effect of maintenance treatment with single agent bevacizumab (18, 19).

GOG-218

This double-blind, placebo-controlled study included 1,873 women with newly diagnosed, epithelial ovarian cancer after debulking surgery (stage III optimal (macroscopic residual disease ≤ 1 cm) or suboptimal (>1 cm) or stage IV). Patients were randomly assigned to one of three treatment groups: six cycles of chemotherapy (carboplatin/paclitaxel every 3 weeks) and concurrent placebo followed by placebo maintenance (arm I), or six cycles of chemotherapy and concurrent bevacizumab (15 mg/kg every 3 weeks) followed by placebo maintenance (arm II), or bevacizumab maintenance (arm III) given for up to 15 months (16 cycles), intolerable toxicity or until pro-

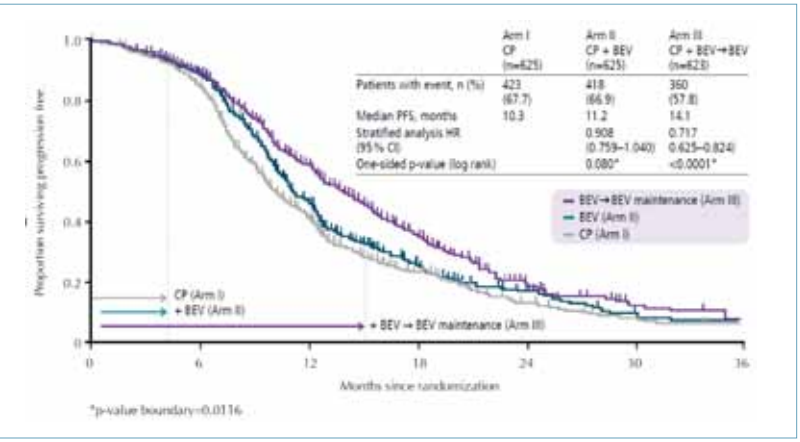


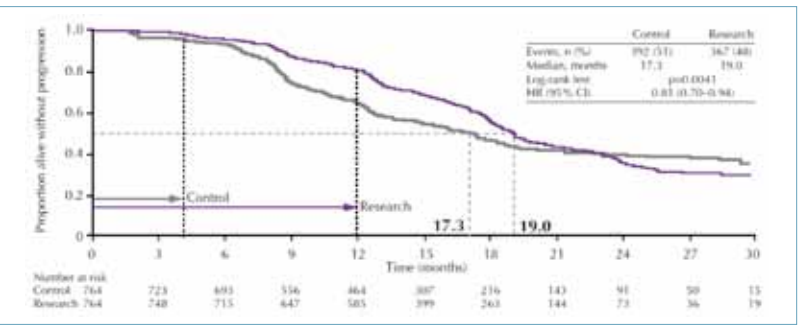
Fig. 1 GOG-218: Academic analysis of PFS

gression. Disease progression was defined based on RECIST, global clinical deterioration, or CA-125.

After a median follow-up of 17.4 months, the primary analysis showed that the median PFS was significantly higher in arm III (14.1 months) than in arm I (10.3 months) (Fig. 1). This translated into a 28% reduction in the risk of progression (median gain of 3.8 months) for concurrent and additional maintenance treatment with bevacizumab (arm III). Compared to chemotherapy alone, the hazard ratio of tumor progression for concurrent and maintenance bevacizumab was 0.717 (95% CI, 0.625–0.824; P<0.0001). There was no significant difference in median PFS between arms II (11.2 month) and I.
A retrospective analysis, censoring for progression events that were solely based on CA-125 elevation, showed that PFS was 6 months longer (18 versus 12 months, P <0.0001). The hazard ratio for progression for concurrent bevacizumab followed by placebo maintenance was 0.908 (95% CI, 0.795–1.04; P = 0.16), i.e. the PFS with concurrent bevacizumab (arm II) was not statistically different from the one with chemotherapy alone (arm I).

The OS analysis conducted at the time of the final PFS analysis did not show any conclusive differences between the three treatments. However, data were not sufficiently mature with roughly 20% of events at the time of the first OS analysis. Mature PFS and OS data are expected in 2012. After tumor progression, treatment was unblinded and cross-over to bevacizumab was possible. If this will confound long-term data evaluation will be seen in the future.

Fig. 2 ICON-7: Academic analysis of PFS



The type and severity of adverse events were similar to those reported with bevacizumab in combination with chemotherapy in the treatment of other metastatic solid tumors (Table 1). There was no increased risk for gastrointestinal perforation and fistula, with rates of less than 3% in all treatment groups.

ICON 7

This open-label study included 1,528 women with newly diagnosed epithelial ovarian cancer. The majority of patients had advanced stage ovarian cancer, but also patients with earlier-stage could be included, representing about 10% of the population in each arm. The patients were randomized to receive either six cycles of chemotherapy alone (carboplatin/paclitaxel every 3 weeks) or with concurrent bevacizumab at 7.5 mg/kg every 3 weeks followed by bevacizumab alone for a further 12 cycles up to 12 months.

Median follow-up at the time of analysis was 19.4 months. Bevacizumab in addition to chemotherapy and continued up to 12 months improved the PFS from a median of 17.3 months to 19.0 months with a hazard ratio of 0.81 (95% CI, 0.70–0.94; P=0.0041, academic analysis) (Fig. 2). Mature data to assess OS and mature PFS data are expected in 2012; at the time of the first analysis only 16% of OS events had occurred. The treatment was well tolerated with no new toxicities reported (Table 1).

GOG-218 and ICON7: Consistent findings from well designed studies but open questions remain

GOG-218 and ICON 7 are two well-designed randomized trials conducted at high quality standards and have enrolled more than 3,300 women with advanced ovarian cancer. There are some differences between the two trials: the most relevant are the design (GOG-0218: double blind; ICON 7: open-label), the dosage of bevacizumab (15 mg/kg; 7.5 mg/kg), the duration of maintenance therapy (15 months; 12 months), the patient population (stage III and IV; high-risk early FIGO stage I, IIa as well as stage III and IV), percent of patients with suboptimal surgery (39%; vs 26%).

Select adverse events, % (grade when limited)	GOG-0218 CP (n=601)	GOG-0218 CP + B15 (n=607)	GOG-0218 CP + B15® B15 (n=608)	ICON7 CP+(n=753)	ICON7 CP + B7.5® B7.5 (n=745)
GI Events (Perforation/fistula/necrosis/leak (grade ≥2))	1.2	2.8	2.6	–	–
Fistula/abscess (grade ≥3)	–	–	–	0.9	0.8
GI perforation (grade ≥3)	–	–	–	0.4	1.3
Hypertension (grade ≥2)	7.2	16.5	22.9	2.1	18.3
Proteinuria (grade ≥3)	0.7	0.7	1.6	0.1	0.5
Pain (grade ≥2)	41.7	41.5	47.5	NR	NR
Neutropenia (grade ≥4)	57.7	63.3	63.3	15.1*	16.5*
Febrile neutropenia (all grades)	3.5	4.9	4.3	2.0	2.8
Venous thromboembolic event (all grades)	5.8	5.3	6.7	4.1	6.7
Arterial thromboembolic event (all grades)	0.8	0.7	0.7	1.5	3.6
CNS bleeding (grade ≥3)	0	0	0.3	NR	NR
Non-CNS bleeding (grade ≥3)	0.8	1.3	2.1	0.3	1.2
RPLS	0	0.2	0.2	0	0

*Neutropenia Grade ≥ 3

Table 1: Selected Adverse Events in GOG-0218 and ICON7

These two studies are so far the only large, randomized phase III trials which have demonstrated an improved PFS with an anti-angiogenic agent in combination with standard chemotherapy in the initial treatment of ovarian cancer.

Several questions still need to be answered. Should bevacizumab be used during the initial part of the treatment as well as in the subsequent maintenance phase? What is the most appropriate dosage and duration of treatment for bevacizumab? Would bevacizumab also add benefit to the weekly paclitaxel regimen, which is not yet regarded as standard? It cannot be concluded from these findings whether inhibition of VEGF may have a greater impact on tumor regrowth in the management of recurrent disease than in the first-line treatment. Mature data on OS and quality of life are awaited.

What are the consequences for clinical practice?

The proof of principle of the effect of anti-angiogenic therapy in ovarian cancer has been confirmed by both GOG 218 and ICON 7. However, additional data from those studies and others are needed to clarify how to best incorporate bevacizumab into the treatment of ovarian cancer. Open questions have been addressed by Roche as well as international gynecological and oncological societies, and both have committed themselves to answer these and other questions in future clinical trials. Until these trials reports are available bevacizumab cannot be considered as initial standard treatment even though the two trials suggest that incorporation of bevacizumab in the control arm of a randomized trial could be a valid option.

It is not possible to define a patient population who could clearly benefit from bevacizumab. The decision to treat a woman with ovarian cancer with bevacizumab can only be made on an individual basis. By contrast, the patients who should not be treated with bevacizumab because of safety concerns include those with:

- uncontrolled hypertension
- a history of thrombosis in the last 6 months or a tendency to develop thrombosis
- symptomatic central nervous system metastases
- recent hemoptysis
- significant cardiovascular disease or cardiac failure
- bleeding disorders
- eligibility for secondary surgery (due to wound-healing complications induced by bevacizumab (if administered less than 4 weeks after surgery))
- extensive bowel involvement
- multiple stenosis
- subileus.

Conclusions

The GOG-218 and ICON 7 studies are examples of high-quality, clinical investigations with international collaboration. ICON 7 validates and extends the observations from GOG-218, confirming that VEGF is an important

driver in ovarian cancer and that bevacizumab is an effective agent with acceptable toxicity. However, the improvements in PFS observed have yet to be associated with improvements in OS or QoL, which are crucial to define the clinical benefit of the treatment.
The most urgent need is to find predictive factors which define the patients who will most likely benefit from adding bevacizumab to standard chemotherapy. Thus clinical trials including translational research questions are of high priority. At present, bevacizumab in combination with carboplatin and paclitaxel cannot be recommended as standard first-line therapy; participation in clinical trials is highly recommended. Treatment decisions for patients who cannot participate in clinical trials must be made on an individual basis.

*Swissmedic granted Bevacizumab the orphan drug status for the treatment of ovarian cancer (21). Bevacizumab for ovarian cancer is not approved in Switzerland (22).

Conflict of interest

The expert meeting where the idea of this publication was discussed as well as the publication itself was supported by Roche Pharma (Schweiz) AG regardless of the use and / or prescription of Roche products. The content of this publication lies completely within the responsibility of the authors.

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